Alcohol septal ablation for obstructive hypertrophic cardiomyopathy

Steggerda, Robbert

Chapter 7.1

Long-Term Outcomes After Medical and Invasive Treatment in Patients With Hypertrophic Cardiomyopathy

Pieter A. Vriesendorp, MD, Max Liebregts, MD, Robbert C. Steggerda, MD, Arend F.L. Schinkel, MD, PHD, Rik Willems, MD, PHD Folkert J. ten Cate, MD, PHD, Johan van Cleemput, MD, PHD, Jurriën M. ten Berg, MD, PHD, Michelle Michels, MD, PHD

JACC Heart Failure 2014; 2: 630-636.

Abstract

Objectives

The aim of this study was to determine the long-term outcomes (all-cause mortality and sudden cardiac death [SCD]) after medical therapy, alcohol septal ablation (ASA), and myectomy in patients with hypertrophic cardio- myopathy (HCM).

BACKGROUND Therapy-resistant obstructive HCM can be treated both surgically and percutaneously. But there is no consensus on the long-term effects of ASA, especially on SCD.

Methods

This study included 1,047 consecutive patients with HCM (mean age 52 ± 16 years, 61% men) from 3 tertiary referral centers. A total of 690 patients (66%) had left ventricular outflow tract gradients < 30 mmHg, of whom 124 (12%) were treated medically, 316 (30%) underwent ASA, and 250 (24%) underwent myectomy. Primary endpoints were all-cause mortality and SCD. Kaplan-Meier graphs and Cox regression models were used for statistical analyses.

Results

The mean follow-up period was 7.6 ± 5.3 years. Ten-year survival was similar in medically treated patients (84%), ASA patients (82%), myectomy patients (85%), and patients with nonobstructive HCM (85%) (log-rank p = 0.50). The annual rate of SCD was low after invasive therapy: 1.0%/year in the ASA group and 0.8%/year in the myectomy group. Multivariate analysis demonstrated that the risk for SCD was lower after myectomy compared with the ASA group (hazard ratio: 2.1; 95% confidence interval: 1.0 to 4.4; p 1⁄4 0.04) and the medical group (hazard ratio: 2.3; 95% confidence interval: 1.0 to 5.2; p = 0.04).

Conclusions

Patients with obstructive HCM who are treated at referral centers for HCM care have good survival and low SCD risk, similar to that of patients with nonobstructive HCM. The SCD risk of patients after myectomy was lower than after ASA or in the medical group.

Hypertrophic cardiomyopathy (HCM) is the most prevalent inheritable myocardial dis- ease, and (provocable) left ventricular
outflow tract (LVOT) obstruction is present in the majority of patients with HCM (±70%) (1). Not only is LVOT obstruction associated with symptoms such as dyspnea on exertion, fatigue, chest pain, and syncope, but previous studies have also demonstrated that the presence of obstruction increases all-cause mortality and the occurrence of sudden cardiac death (SCD) in these patients (2,3), and it is included as a risk factor in the novel clinical risk prediction model presented by the HCM Outcomes Investigators (4).

Therapy-resistant obstructive HCM can be treated both surgically and percutaneously, and in recent years there has been an intense and polarizing debate to define the best strategy (5–8). Surgical approaches have been used for more than 5 decades, and at experienced centers, relief of obstruction can be achieved with minimal perioperative morbidity and mortality (9–11). However, myectomy is open-heart surgery with relatively long rehabilitation, so in 1995, alcohol septal ablation (ASA), a percutaneous alternative, was developed (12). This strategy was quickly adopted all over the world, and patients who underwent ASA quickly outnumbered those who underwent myectomy (5–8,12,13). In some European countries, ASA has fully replaced myectomy (7). Concerns about ASA remain, however, especially about the arrhythmogenic effect of the ablation scar in patients already at increased risk for life-threatening arrhythmias (14–17).

Although a randomized controlled trial does not seem feasible (18), and recent meta-analyses (19,20) evaluated only short-term SCD rate and survival, there is no consensus on the long-term outcomes of ASA (17,21–24). The aim of the present study was therefore to determine the long-term effects of medical treatment, ASA, and myectomy on all-cause mortality and SCD.

Methods

Study design and population.

An international multicenter, observational cohort design was used. The study conformed to the principles of the Declaration of Helsinki. All patients gave informed consent for the intervention, and local institutional review board approval was obtained.

The study population consisted of 1,065 consecutive patients with HCM from University Hospital Leuven (Leuven, Belgium; n = 200), St. Antonius Hospital Nieuwegein (Nieuwegein, the Netherlands; n = 318), and Thoraxcenter, Erasmus Medical Center

(Rotterdam, the Netherlands; n = 547). Each patient had an established diagnosis of HCM, based on unexplained left ventricular hypertrophy of ≥15 mm, assessed by echocardiography (25,26). Patients with HCM linked to Noonan's syndrome, Fabry's disease, mitochondrial disease, or congenital heart defects were excluded.

The LVOT gradient was measured in all patients using continuous-wave Doppler echocardiography, at rest and after provocative maneuvers. Patients were considered to have obstructive HCM if the LVOT gradient was ≥ 30 mm Hg, at rest or after provocation. Invasive therapy was indicated if the peak LVOT gradient was ≥ 50 mm Hg, ventricular septal thickness was ≥ 15 mm, and there was persistent New York Heart Association (NYHA) functional class III or IV dyspnea or Canadian Cardio- vascular Society class III or IV angina despite optimal medical therapy (26). Patients without LVOT gradients ≥ 30 mmHg after provocation were considered to have nonobstructive HCM and used as a control group. Patients with obstructive HCM were classified in 3 groups on the basis of the clinical treatment strategy: a medically treated group, an ASA group, and a myectomy group. Surgical septal myectomy was performed throughout the study period and as described previously (27,28), and postoperative care was in accordance with local protocols. ASA was performed starting from 1999 as described previously (28,29). Afterward, all patients were monitored for at least 24 h in the intensive coronary care unit.

Endpoints

The primary endpoints of this study were all-cause mortality and SCD-related events. The SCD endpoint was a composite endpoint consisting of: 1) instantaneous and unexpected death within 1 h of witnessed collapse in patients who were previously in stable clinical condition, or nocturnal death with no antecedent history of worsening symptoms; 2) successful resuscitation after cardiac arrest; 3) appropriate implantable cardioverter-defibrillator (ICD) intervention for ventricular fibrillation or for fast ventricular tachycardia (>200 beats/min); and 4) unknown cause of death. Unknown death was included in the SCD endpoint to estimate the maximal occurrence of SCD in the population. We also evaluated periprocedural arrhythmic events and mortality, reinterventions, LVOT gradient reduction, and implantation of ICDs.

Mortality and adverse events were retrieved from hospital patient records at the center at which follow- up occurred, from civil service population registers, and from information provided by patients them- selves or their general practitioners. Cardiac trans- plantation was

considered an HCM-related death, and patients were censored at the time of transplantation. All ICD interventions were evaluated by an experienced electrophysiologist.

Data collection and follow-up.

Follow-up started at the time of intervention. In the medically treated cohort, follow-up started at the first outpatient clinic contact after January 1, 1990. At baseline, all patients were evaluated for the following characteristics: NYHA class, maximal left ventricular wall thickness, maximal (provocable) LVOT gradient, systolic and diastolic left ventricular function, and medications used. During follow-up, the established risk factors for SCD were evaluated (25,26). Other potential modifiers of SCD risk were also examined: atrial fibrillation and coronary artery disease. In patients treated with ASA, the dose of alcohol used was also collected.

If no endpoints occurred during follow-up, the final censoring date was set at November 1, 2012. If alternative septal reduction therapy was necessary (e.g., ASA after myectomy or vice versa), follow-up was censored at the date of the second intervention, because of the difficulty attributing any later event to any intervention.

Statistical analysis

SPSS version 20 (IBM, Armonk, New York) and Excel 2010 (Microsoft Corporation, Redmond, Washington) were used for all statistical analyses. Categorical variables are summarized as percentages. Normality was assessed using the Shapiro-Wilk test combined with visual inspection of histograms and Q-Q plots. Normally distributed continuous data are expressed as mean ± SD and non- normally distributed data as median (interquartile range [IQR]). To compare continuous variables, Student t tests, Mann-Whitney U tests, and one-way analysis of variance were used. When appropriate, post hoc comparisons were carried out using Bonferroni correction. To compare categorical variables, chi-square tests were used. To identify clinical predictors of SCD mortality, univariate and multivariate Cox regression analyses were used. Variables were selected for multivariate analysis if univariate p values were <0.10 and are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The final number of variables was restricted according to the number of endpoint events to avoid overfitting the multivariate model. All tests were 2 sided, and p values <0.05 were considered statistically significant.

Results

Baseline characteristics

Table 1 lists the baseline characteristics of all patients. Of the 1,065 patients (mean age 52 ± 16 years, 61% men) included in this study, 716 (67%) had obstructive HCM; in 269 (25%), LVOT obstruction was present only after provocation. Of these 716 patients, 142 (20%) were treated medically, 321 (45%) underwent ASA, and 253 (35%) underwent myectomy. Patients in the ASA group were older (58 ± 14 years) than those in the surgery group (52 ± 16 years, p < 0.001) and in the medical group (53 ± 15 years, p = 0.001). The majority of medically treated patients (n = 124 [87%]) reported no symptoms or mild (NYHA functional class I or II) symptoms at baseline, despite a mean LVOT gradient of 70 ± 32 mm Hg. The other 18 patients (13%) had indications for invasive treatment but were considered not eligible because of severe comorbidities (e.g., 1 patient had liver cirrhosis due to alcohol abuse and kidney failure) or patient refusal (several patients refused further invasive treatment, mostly because they were at old age and preferred no further interventions). In this group, mortality was high (8 deaths [44%]), and these patients were excluded from further analysis.

The distribution of established risk factors for SCD, among the 3 intervention groups and controls, is shown in Table 1. Complete risk stratification was not available for all patients: blood pressure response during exercise testing was available in 645 patients (61%), and documented rhythm information was available in 656 patients (62%). Significantly more patients in the myectomy group (n = 44 [17%]) had ≥ 2 established risk factors for SCD than those in ASA group (n = 32 [10%]) (p 1⁄4 0.009).

Table 1 Baseline Characteristics of 1065 Patients With HCM

Variable	**Medical group**	**ASA group**	**Myectomy group**	**Control (non-obstructive) group**
n=	*(n=142)*	*(n=321)*	*(n=253)*	*(n=349)*
Age (yrs)	53 ± 15‡	58 ± 14‡	52 ± 16‡	46 ± 16
Women	54 (38%)*	143 (45%)‡	117 (46%)‡	98 (28%)
NYHA class III or IV	18 (13%)	249 (78%)‡	165 (65%)‡	40 (11%)
Atrial fibrillation	21 (15%)†	76 (24%)	62 (25%)	103 (30%)
Coronary artery disease	4 (3%)	18 (6%)†	25 (10%)†	12 (3%)
Maximal LVWT (mm)	20 ± 5	21 ± 5‡	21 ± 5‡	20 ± 5
LVOT gradient (mm Hg)	70 ± 32‡	102 ± 52‡	92 ± 39‡	9 ± 6
Systolic dysfunction (EF <50%)	17 (12%)	18 (6%)‡	18 (7%)‡	63 (18%)
Diastolic dysfunction	99 (70%)†	130 (40%)‡	105 (42%)†	190 (54%)
Medications				
Beta-receptor antagonists	83 (58%)*	218 (68%)‡	167 (66%)‡	166 (48%)
Calcium-channel blockers	47 (33%)‡	116 (36%)‡	90 (36%)‡	49 (14%)
Risk factors				
Survivor of SCD	4 (3%)*	7 (2%)‡	8 (3%)*	29 (8%)
Sudden death in family history	23 (16%)	24 (7%)‡	42 (17%)	81 (23%)
Abnormal BP response	9 (6%)	31 (10%)	37 (15%)	29 (8%)
Maximal LVWT >30 mm	9 (6%)	22 (7%)	18 (7%)	19 (5%)
Nonsustained VT	22 (15%)†	41 (13%)‡	37 (15%)	98 (28%)
Syncope	10 (7%)	52 (16%)	41 (16%)	45 (12%)
0 risk factors	87 (61%)†	188 (59%)†	136 (54%)*	158 (45%)
≥2 risk factors	15 (11%)*	32 (10%)†	44 (17%)	66 (19%)

Values are mean ± SD or n (%).

ASA = alcohol septal ablation; BP = blood pressure; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; LVOT = left ventricular outflow tract; LVWT = left ventricular wall thickness; NYHA = New York Heart Association; SCD = sudden cardiac death; VT = ventricular tachycardia.

∗$p < 0.05$, †$p < 0.01$, and ‡$p < 0.001$ compared with controls.

Procedural data.

Invasive therapy was performed in 574 patients with obstructive HCM. Periprocedural mortality was similar between ASA (n 1⁄4 5 [1.6%]) and myectomy (n 1⁄4 3 [1.2%]) (p 1⁄4 0.70). In the first 30 days post-procedure, ventricular ar- rhythmias occurred more frequently in the ASA group (n 1⁄4 11 [3.1%]) than in the myectomy group (n 1⁄4 1 [0.4%]) ($p < 0.001$). Cardiac resuscitation was neces- sary in 7 ASA patients (2.2%). Residual LVOT gradient was measured after 3 months and was reduced after both ASA and myectomy: from a median of 97 mm Hg (IQR: 66 to 130 mm Hg) to 10 mm Hg (IQR: 1 to 24 mm Hg) after ASA, and from a median of 90 mm Hg (IQR: 70 to 100 mm Hg) to 9 mm Hg (IQR: 0 to 16 mm Hg) after myectomy. In 31 ASA patients (9.7%), additional septal reduction therapy was necessary, and this was higher than after myectomy (n 1⁄4 6 [2.3%], $p < 0.001$) (Table 2).

Table 2 Invasive Therapy in 574 patients with HCM

Variable	**ASA** *(n =321)*	**Myectomy** *(n = 253)*
Center		
Leuven	18 (6%)	28 (11%)
Nieuwegein	209 (65%)	109 (43%)
Rotterdam	94 (29%)	116 (46%)
Procedural details		
Volume of alcohol injected (ml)	2.0 (1.0)∗	NA
Residual LVOT gradient (mm Hg)	10 (24)	9 (16)†
Reduction in LVOT gradient (%)	87 ± 30	90 ± 19†
Redo septal reduction therapy	31 (9.7%)	6 (2.3%)‡
Periprocedural arrhythmic event		
Total	11 (3.1%)	1 (0.4%)‡
SCD	3 (0.9%)	1 (0.4%)
Sustained VT	1 (0.3%)	0 (0%)
Resuscitated cardiac arrest	7 (2.2%)	0 (0%)
Periprocedural mortality		
Total	5 (1.6%)	3 (1.2%)
SCD	3 (0.9%)	1 (0.4%)
Heart failure death	0 (0%)	2 (0.8%)
Cardiac tamponade	2 (0.6%)	0

Values are n (%) or mean ± SD.
NA = not applicable; other abbreviations as in Table 1.
∗In 53 patients (16.5%), the dose of alcohol could not be retrieved.
†$p < 0.01$.
‡$p < 0.001$.

Mortality

In 1,047 patients, mean follow-up duration was 7.5 ± 5.3 years (maximum 22.8 years). There were 156 deaths in the entire cohort (Table 3): 8 (5%) were procedure related, 80 (51%) were HCM related, 56 (36%) patients died of noncardiac causes, and causes of death were unknown in 12 (8%). Twelve patients underwent cardiac transplantation and were considered as HCM-related death. Kaplan-Meier estimates of survival are shown in Figure 1A. Five-year and 10-year survival was similar after ASA, myectomy, and medical treatment in patients in NYHA class I or II and those with nonobstructive HCM (Table 3). Independent predictors of all-cause mortality were age (HR: 1.05; 95% CI: 1.0 to 1.1; $p < 0.001$); systolic dysfunction, with ejection fraction <50% (HR: 1.8; 95% CI: 1.2 to 2.6; $p = 0.005$); and a trend toward diastolic dysfunction (HR: 1.4; 95% CI: 0.98 to 1.88; $p = 0.07$) (Table 4).

Table 3 Mortality and SCD in 1047 Patients with HCM

Variable	Medical Treatment (n = 142)	ASA (n = 316)	Myectomy (n = 249)	Control (Nonobstructive HCM) (n = 349)
Follow-up (yrs)	7.1 ± 4.8*	6.3 ± 3.6†	7.9 ± 6.1	8.7 ± 5.7
Mortality				
Periprodecural death	—	5 (1.6%)	3 (1.2%)	-
HCM-related death	11 (8.9%)	12 (3.7%)‡	21 (8.4%)	36 (10.3%)
Noncardiac death	8 (6.5%)	23 (7.2%)*	12 (4.8%)	13 (3.7%)
Unknown death	0 (0%)	3 (0.9%)	6 (2.4%)	3 (0.8%)
Total	19 (15.3%)	38 (11.8%)	39 (15.6%)	52 (14.9%)
5-yr survival	89%	91%	92%	95%
10-yr survival	84%	82%	85%	85%
SCD				
SCD	5 (4.0%)	6 (1.9%)	6 (2.4%)	9 (2.6%)
Resuscitated CA	1 (0.8%)	2 (0.6%)*	2 (0.8%)	9 (2.6%)
Appropriate ICD shock	5 (4.0%)	8 (2.5%)	1 (0.4%)	12 (3.4%)
Unknown death	0 (0%)	3 (0.9%)	6 (2.4%)	3 (0.8%)
Total	11 (8.9%)	19 (6.0%)	15 (6.0%)	31 (8.9%)
Annual SCD rate, %/year	1.26	0.96	0.75	1.02
ICD recipients	14 (11.3%)‡	41 (13.0%)†	29 (11.6%)‡	83 (23.8%)

Values are mean ± SD or n (%).

CA = cardiac arrest; ICD = implantable cardioverter-defibrillator; other abbreviations as in Table 1.

∗$p < 0.05$.

†$p < 0.001$ compared with controls.

‡$p < 0.01$.

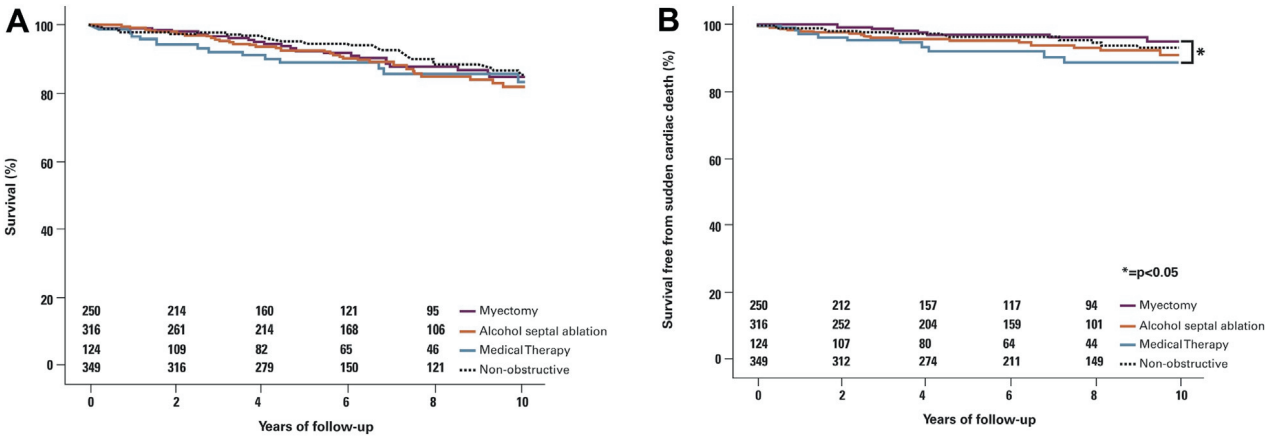
Table 4 Analysis of Clinical Variables Associated with SCD and All-cause Mortality in 1047 Patients With HCM

	Univariate			*Multivariate*		
Variable	HR	CI 95%	*p Value*	HR	CI 95%	*p Value*
Mortality (n = 156)						
Age	1.05	1.03–1.06	<0.001	1.05	1.04–1.06	<0.001
Female	1.8	1.27–2.43	0.001	1.3	0.93–1.79	0.1
Atrial fibrillation	1.6	1.18–2.29	0.003	1.2	0.89–1.78	0.2
Coronary artery disease	1.9	1.25–2.74	0.002	1.4	0.94–2.08	0.1
Systolic dysfunction (EF <50%)	2.2	1.51–3.22	<0.001	1.4	1.19–2.59	0.005
Diastolic dysfunction	1.5	1.08–2.07	0.02	1.8	0.98–1.89	0.07
Myectomy (reference)	1.0		—	1.0		—
ASA	1.3	0.79–2.02	0.3	1.0	0.65–1.61	0.9
Medical therapy (NYHA class I or II)	1.3	0.73–2.20	0.4	1.2	0.68–2.13	0.5
SCD (n = 76)						
Age (yrs)	1.00	0.98–1.01	0.7			
Male	1.6	0.98–2.68	0.06	1.6	0.97–2.73	0.06
LVWT	1.03	0.98–1.08	0.2			
Atrial fibrillation	1.8	1.14–2.87	0.01	1.7	1.06–2.75	0.03
Coronary artery disease	1.8	1.06–3.20	0.03	1.7	0.98–3.04	0.06
SCD survivor	6.5	3.82–10.9	<0.001	6.0	3.43–10.7	<0.001
≥2 established risk factors	3.3	2.04–5.23	<0.001	2.7	1.65–4.44	<0.001
Myectomy (reference)	1.0		—	1.0		—
ASA	2.0	0.99–4.25	0.05	2.1	1.02–4.39	0.04
Medical therapy (NYHA class I or II)	2.2	0.99–4.91	0.05	2.3	1.03–5.19	0.04

Backward multivariate Cox regression analysis was used.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

Figure 1 Survival in 1047 patients with HCM



Kaplan-Meier graphs of survival (A) and survival free of sudden cardiac death (B) in 1,047 patients with hypertrophic cardiomyopathy (HCM)

SCD.
The SCD endpoint occurred in 76 patients over 8,003 patient-years (0.9%/year). The annual SCD rate was 0.96%/year after ASA, 0.76%/year after myectomy, 1.26%/year in medically treated groups, and 1.02%/year in nonobstructive HCM patients (p = 0.40). Appropriate ICD shocks were more common after ASA (in 8 of 41 patients [20%]) than after myectomy (in 1 of 29 patients [3.4%]) (p = 0.03). Other characteristics of SCD are described in Table 3. Kaplan-Meier estimates of survival free from SCD are shown in Figure 1B. Multivariate analysis identified the following independent predictors of SCD: patients who survived ventricular fibrillation or sustained ventricular tachycardia (HR: 6.0; 95% CI: 3.4 to 10.6; p < 0.001), patients with >2 established risk factors (HR: 2.7; 95% CI: 1.6 to 4.4; p < 0.001), patients with atrial fibrillation (HR: 1.7; 95% CI: 1.1 to 2.8; p 1⁄4 0.03), and, when compared with myectomy, ASA (HR: 2.1; 95% CI: 1.0 to 4.4; p = 0.04) and medically treatment (HR: 2.3; 95% CI: 1.1 to 5.1; p 1⁄4 0.04) (Table 4).

Discussion

The purpose of this investigation was to compare the long-term effects of medical treatment, ASA, and myectomy on all-cause mortality and SCD in patients with obstructive HCM. There were 2 important results. First, the mortality rates in patients with prior ASA or myectomy and in medically treated patients in NYHA functional class I or II were similar to those in patients with nonobstructive HCM. Second, the long- term risk for SCD was low after both myectomy (0.8%/year) and ASA (1.0%/year), a small but signifi- cant difference (HR for SCD after ASA vs. myectomy: 2.1; p = 0.04).

Low Mortality in patients with obstructive HCM

The observed survival after both myectomy (10-year survival 85%) and ASA (10-year survival 82%) (p = 0.50) was similar to that in patients with nonobstructive HCM (85%) (p = 0.70 and p = 0.20, respectively). This demonstrates that the survival disadvantage associated with LVOT obstruction can be effectively annulled by appropriate invasive therapy and management at referral centers for HCM care (2). ASA was performed in carefully selected patients who were older and had more comorbidities (61% of the deaths were due to noncardiac causes), but despite this, the observed mortality after ASA was not significantly higher than in the other groups. The observed survival after invasive therapy in this study confirms other studies evaluating long-term outcomes for the individual approaches (21-24) The good survival of patients with obstructive HCM who remained in NYHA class I or II on

optimal medical therapy (10-year survival 84%) could imply that earlier intervention in asymptomatic or mildly symptomatic patients with obstructive HCM is not indicated, despite the low procedural mortality and morbidity of both invasive therapies. Mortality, not surprisingly, was high (44%) in a limited group of patients (n = 18 [13%]) with indications for invasive treatment (NYHA class III or IV despite optimal medical therapy) but who were deemed to be ineligible because of severe comorbidities.

SCD After ASA

Since the introduction of ASA, there have been concerns regarding the arrhythmogenic effect of the ablation scar in patients already at increased risk for life-threatening arrhythmias. Studies of short-term follow-up after ASA have described frequent episodes of sustained ventricular tachycardia and ventricular fibrillation (14, 15, 16 and 17). Our findings confirm this and show that although arrhythmic events were more frequent after ASA (3.1%) than after myectomy (0.4%) ($p < 0.001$), this had no effect on procedure-related mortality (1.6% vs. 1.2%, $p = 0.70$). The aim of this study was to assess the long-term effects of the different treatment modalities, especially because the long-term effect of ASA on SCD is unclear. Two meta-analyses showed that the risk for SCD was not higher in ASA patients than in patients who underwent myectomy. These studies did not focus on long-term outcomes: the mean follow-up period across the cohorts in a study by Agarwal et al. (19) was <3 years, and in a study by Leonardi et al. (20), there was a significant difference in follow-up duration between the ASA and myectomy cohorts, with median follow-up durations of 1,266 patient-years in the myectomy studies and 51 patient-years in the ASA studies. Other concerns, especially about the calculated SCD risk, have already been illustrated by Nishimura and Ommen (30). The risk for SCD after myectomy has generally been low (11), and the study by McLeod et al. (31) even suggests that myectomy could decrease the risk for SCD.

Our study found that the annual SCD rate (excluding periprocedural events) in patients who underwent ASA was 1.0%/year, which was similar to that in patients with nonobstructive HCM and medically treated patients. A study by ten Cate et al. (17), which included a subset of the patients from the present study, reported a higher SCD rate than this study. The reason for this is 2-fold: 1) a separate endpoint for SCD (instead of a composite of cardiac mortality and SCD) was used, and 2) we excluded periprocedural events from the final analysis to focus on the long-term effects of ASA. Two recently published studies with long-term follow-up found that the risk for SCD was not high after ASA. Jensen et al. (23) examined 470 ASA

patients, with a mean follow- up period of 8.4 years, and found an annual SCD rate of 0.5%/year. Sorajja et al. (24) examined 177 ASA patients and 177 age- and sex-matched myectomy patients, with a mean follow-up period of 5.7 years. They found annual SCD rates (including unknown death) of 1.3%/year after ASA and 1.1%/year after myectomy. The results of this study are in line with these findings, but the SCD risk after ASA is still higher than after myectomy (0.8%/year; HR for SCD after ASA vs. myectomy: 2.1; $p = 0.04$).

Patient selection and specialised care

The present findings may have implications for the clinical management of patients with obstructive HCM who are considered for septal reduction therapy. Patients who underwent myectomy had a statistically significantly lower risk for SCD compared with patients who underwent ASA.

This, combined with a lower need for additional septal reduction therapy and lower periprocedural arrhythmic events, favors surgical myectomy over ASA when an invasive strategy is chosen, for example, in younger and otherwise healthy patients. In older patients or patients with comorbidities and drug-refractory symptoms, and appropriate septal anatomy, the expected survival after ASA is excellent, and in these patients, ASA is a valuable therapy. Open-heart surgery can be avoided, and rehabilitation is much faster. We recommend that a multi- disciplinary heart team (consisting of at least a cardiothoracic surgeon, an interventional cardiolo- gist, and a cardiologist specializing in the care of pa- tients with HCM) determines the optimal strategy for septal reduction. Also, in line with the 2003 European Society of Cardiology and American College of Car- diology (25) and 2011 American College of Cardiology Foundation and American Heart Association (26) guidelines, the procedure should be performed by experienced operators and confined to centers with substantial and specific experience with HCM care.

Study limitations

This study had several limitations. The 3 centers are all tertiary referral centers for the diagnostic and therapeutic care of patients with HCM, and the patient population might not represent the general HCM population. This referral and selec- tion bias could have influenced the results. Data collection was limited to variables that were routinely collected. Because rhythm documentation of the event was not available for all SCD cases, it was not

possible to ascertain that all deaths were arrhythmic in nature. Neither was it possible to correct for individual or local alterations of surgical or percutaneous technique, but all procedures were performed by experienced interventional cardiologists or cardio- thoracic surgeons. This implies that our findings are more generalizable than those of single-center investigations.

Conclusions

Patients with obstructive HCM who are treated at referral centers for HCM care have good survival and low SCD risk, similar to that of patients with nonobstructive HCM. The SCD risk in patients after myectomy was lower than that after ASA and in the medical group.

Acknowledgements

The authors thank D.A.M.J. Theuns, O.I.I. Soliman, R.T. van Domburg, H. Heid- buchel, P.L. de Jong, A.J. Hauer, and J.C. Balt and all treating physicians for providing additional data and assisting the authors in the realization of this study.

Reference List

1. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruc- tion. Circulation 2006;114:2232–9.
2. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295–303.
3. Elliott PM, Gimeno JR, Tome MT, et al. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardio- myopathy. Eur Heart J 2006;27:1933–41.
4. O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk- SCD). Eur Heart J 2014;35:2010–20.
5. Maron BJ. Controversies in cardiovascular medicine. Surgical myectomy remains the primary treatment option for severely symptomatic patients with obstructive hypertrophic cardiomy- opathy. Circulation 2007;116:196–206.
6. Fifer MA. Controversies in cardiovascular med- icine. Most fully informed patients choose septal ablation over septal myectomy. Circulation 2007; 116:207–16.
7. Maron BJ, Yacoub M, Dearani JA. Controversies in cardiovascular medicine. Benefits of surgery in obstructive hypertrophic cardiomyopathy: bring septal myectomy back for European patients. Eur Heart J 2011;32:1055–8.
8. Fifer MA, Sigwart U. Controversies in cardio- vascular medicine. Hypertrophic obstructive cardiomyopathy: alcohol septal ablation. Eur Heart J 2011;32:1059–64.
9. Kirklin JW, Ellis FH Jr. Surgical relief of diffuse subvalvular aortic stenosis. Circulation 1961;24: 739–42.
10. Morrow AG, Reitz BA, Epstein SE, et al. Operative treatment in hypertrophic subaortic stenosis. Techniques, and the results of pre and postoperative assessments in 83 patients. Circu- lation 1975;52:88–102.
11.Ommen SR, Maron BJ, Olivotto I, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470–6.
12. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995;346:211–4.
13. Rigopoulos AG, Seggewiss H. A decade of percutaneous septal ablation in hypertrophic cardiomyopathy. Circ J 2011;75:28–37.

14. Boltwood CM Jr., Chien W, Ports T. Ventricular tachycardia complicating alcohol septal ablation. N Engl J Med 2004;351:1914–5.
15. Kuhn H, Lawrenz T, Lieder F, et al. Survival after transcoronary ablation of septal hypertro- phy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience. Clin Res Cardiol 2008;97:234–43.
16. Sorajja P, Valeti U, Nishimura RA, et al. Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation 2008; 118:131–9.
17. ten Cate FJ, Soliman OI, Michels M, et al. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomy- opathy: a word of caution. Circ Heart Fail 2010;3: 362–9.
18. Olivotto I, Ommen SR, Maron MS, Cecchi F, Maron BJ. Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic car- diomyopathy. Will there ever be a randomized trial? J Am Coll Cardiol 2007;50:831–4.
19. Agarwal S, Tuzcu EM, Desai MY, et al. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;55:823–34.
20. Leonardi RA, Kransdorf EP, Simel DL, Wang A. Meta-analyses of septal reduction therapies for obstructive hypertrophic cardiomyopathy: comparative rates of overall mortality and sudden cardiac death after treatment. Circ Cardiovasc Interv 2010;3:97–104.
21. Ball W, Ivanov J, Rakowski H, et al. Long-term survival in patients with resting obstructive hypertrophic cardiomyopathy comparison of con- servative versus invasive treatment. J Am Coll Cardiol 2011;58:2313–21.
22. Nagueh SF, Groves BM, Schwartz L, et al. Alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy. A multicenter North American registry. J Am Coll Cardiol 2011;58:2322–8.
23. Jensen MK, Prinz C, Horstkotte D, et al. Alcohol septal ablation in patients with hypertro- phic obstructive cardiomyopathy: low incidence of sudden cardiac death and reduced risk profile. Heart 2013;99:1012–7.
24. Sorajja P, Ommen SR, Holmes DR, et al. Sur- vival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation 2012; 126:2374–80.
25. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy—a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Commit- tee for Practice Guidelines. European Heart Jour- nal 2003;24:1965–91.

26. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treat- ment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Associa- tion Task Force on Practice Guidelines. J Am Coll Cardiol 2011;58:2703–38.
27. Maat LP, Slager CJ, van Herwerden LA, et al. Spark erosion myectomy in hypertrophic obstruc- tive cardiomyopathy. Ann Thorac Surg 1994;58: 536–40.
28. van der Lee C, ten Cate FJ, Geleijnse ML, et al. Percutaneous versus surgical treatment for patients with hypertrophic obstructive cardiomy- opathy and enlarged anterior mitral valve leaflets. Circulation 2005;112:482–8.
29. van der Lee C, Scholzel B, ten Berg JM, et al. Usefulness of clinical, echocardiographic, and procedural characteristics to predict outcome after percutaneous transluminal septal myocardial ablation. Am J Cardiol 2008;101:1315–20.
30. Nishimura RA, Ommen SR. Septal reduc- tion therapy for obstructive hypertrophic car- diomyopathy and sudden death: what statistics cannot tell you. Circ Cardiovasc Interv 2010;3: 91–3.
31. McLeod CJ, Ommen SR, Ackerman MJ, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defi- brillator discharge in obstructive hypertro- phic cardiomyopathy. Eur Heart J 2007;28: 2583–8.